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Effects of Dexmedetomidine on Postoperative Recovery Profile after Sevoflurane Anesthesia in Pediatric Patients: A Meta-analysis

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Abstract

Objective: We aim to evaluate whether dexmedetomidine can reduce incidence caused by sevoflurane anesthesia in pediatric patients systematically.

Methods: We have searched the Cochrane Library, PubMed, EBSCO, Springer, Chinese Journal Full-text Database (CNKI), Chinese Biomedical Literature Database (CBM) and WanFang Data (all the materials selected from these databases range from the date of establishment of the databases to April 2013). Reference lists of all studies have also been checked. Two valuators performed the process of RCT, quality assessment, and data extraction with inclusion and exclusion criteria, and conduct the Meta-analysis with the software RevMan5.2.

Results: The meta-analysis which including 27 randomized trials and 1882 children showed that dexmedetomidine extended the incidence of the children's recovery time [MD=2.39, 95% CI (1.27, 3.51)] and discharge time [MD=6.09, 95% CI (3.42, 8.77)] compared with placebo. Nevertheless, there were no obvious differences in extubation time [MD=0.75, 95% CI (0.45, 1.05)]. While reducing the incidence of early emergence agitation, dexmedetomidine showed a large advantage [RR=0.31, 95% CI (0.26, 0.38)] and could reduce agitation score [MD=-0.89, 95% CI (-1.04, -0.74)], also could reduce pain score [MD=-2.66, 95% CI (-3.81, -1.51)], as well as the need for painkillers [RR=0.34, 95% CI (0.22, 0.52)]. What's more, on reducing occurrence of nausea and vomiting [RR=0.59, 95% CI (0.36, 0.97)], occurrence of bucking [RR=0.39, 95% CI (0.23, 0.68)], dexmedetomidine also showed some preventive effects. There were no serious side effects on respiratory and circulatory system in all included studies.

Conclusion: Dexmedetomidine can be used safely in children and improve the awakening quality after sevoflurane anesthesia.

Keywords: Dexmedetomidine; Sevoflurane anesthesia; Child; Recovery period; Agitation; Meta-analysis

Introduction

Sevoflurane is a popular inhalational anesthetic for general anesthesia in children. It is especially characterized by a lower blood/gas partition coefficient, less irritation to the airway, less cardio depressive effect, lower hepatotoxicity and easier to obtain with children as compared with other volatile anesthetics. Anesthesiologists prefer those characteristics for pediatric use. However, concern has been raised over its propensity to cause significant emergence agitation and other adverse reactions during the immediate recovery phase of sevoflurane anesthesia [1,2]. Theoretically, Dexmedetomidine (DEX) is a new type of highly selective alpha2-adrenergic receptor agonist with sedative, analgesic, anti-sympathetic activity, and has minor respiratory inhibition, but the safety and efficacy of DEX in pediatric patients below 18 years old is still not clear in its package insert. Here in this case, whether dexmedetomidine can safely and effectively improve the children' wake quality remains uncertain. According to the methods of the Cochrane systematic review, we reviewed the Randomized Controlled Trials (RCTs) about dexmedetomidine for prevention of emergence agitation and other side effects in pediatric patients after sevoflurane anesthesia. These data are either in English or non-English language publications, and the main purpose of this meta-analysis is to evaluate whether dexmedetomidine can reduce postoperative agitation and other adverse reactions in children, thereby improve the quality of awakening, and provide an important basis for the clinical application and further research.

Materials and Methods

Inclusion and exclusion criteria

Inclusion criteria: The type of research: clinical Randomized Controlled Trials (RCTs). Research object: the children who are below 12 years old received sevoflurane anesthesia. The children had no neurological disorders and behavioral disorders before operation. Intervention measures: experimental group, intravenous dexmedetomidine; control group only received placebo.

Exclusion criteria: Case reports with sample size of less than 10 studies. Simply medical examination rather than a surgical operation. Repeat published literature those that cannot obtain data directly or indirectly.

Systematic search and strategy

A systemic search of the relevant literature was performed without any language limitation restricted to RCTs available in English. We searched the Cochrane Library, PubMed, EBSCO, Springer, Chinese Journal Full-text Database (CNKI), Chinese Biomedical Literature Database (CBM) and WanFang Data (all the materials selected from these databases range from the date of establishment of the databases to April 2013). Reference lists of all studies have also been checked.

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Published articles contained key words such as "dexmedetomidine", "α2-adrenoceptoragonist", "sevoflurane", "anesthesia", "pediatric", "children", "postanesthesia", "postoperative", "PACU", "Recovery Room", "restlessness", "agitation", "delirium" in their titles or abstracts. The search strategy consisted of a combination of free text words such as: "dexmedetomidine or α2-adrenoceptor agonist" and "sevoflurane" and "children or pediatric" and "Recovery or postanesthesia or restlessness or agitation or delirium".

Data extraction and quality assessment

The two valuators independently categorized these data by reading the citations, abstracts and qualified the data left using a standardized data extraction by going through the whole article. A third reviewer resolved all the disagreements. If data needed clarification, we contacted the original authors.

The quality of each study was assessed according to the modified Jadad scale score, we assessed whether the patients were randomly assigned, whether the randomization procedures were appropriate, whether the study was double-blinded, whether the blinding was appropriate and whether the authors reported the numbers and reasons for dropouts. The study with the modified Jadad score 1 to 3 was divided into low-quality literature, and 4 to 7 was divided into high-quality literature.

Statistical analysis

The software package RevMan 5.2 provided by the Cochrane

First author and year	Patient age(years)	Surgery type	D/C (No. of patients)	Intervention		Main outcome measures	New Jadad score
				Dexmedetomidine group	Control group		
O¨zcengiz [3] 2011	3~9	esophageal dilatation procedures	25/25	DEX 2.5 μg/kg, given orally	saline	⑤	6
Erdil [4] 2009	2~7	adenoidectomy	30/30	DEX 0.5 μg/kg IV after tracheal intubation	saline	①②⑤⑥	6
Guler [5] 2005	3~7	adenotonsillectomy	30/30	DEX 0.5 μg/kg IV,5 min before the end of surgery	placebo	①②④⑤⑥	6
Jia-Yao [6] 2013	2~7	strabismus surgery	27/24	DEX 1 μg/kg, IV	saline	②③⑤⑥	7
Masami [7] 2010	1~9	same-day surgery or over-night stay surgery	39/42	DEX 0.3 μg/kg IV over 10 min after anesthetic induction	saline	③⑤⑥	6
Shukry [8] 2005	1~10	outpatient surgical procedures	23/23	A continuous perioperative infusion of 0.2 μg/kg/h DEX	saline	②③⑤⑥	7
Mauricio E [9] 2004	1~10	Inguinal hernia repair and circumcision	60/30	DEX 0.15 μg/kg OR 0.3 μg/kg IV after anesthetic induction	saline	①③⑤	6
Nidhi [10] 2013	8~12	spinal dysraphism	18/18	loading dose: DEX 1 μg/kg, 0.5 μg/kg/h to maintain	saline	①②⑤⑥	7
Qing-tao [11] 2012	5~13	tonsillectomy	80/40	loading dose: DEX 0.5 μg/kg	lactated Ringer's	①②③⑤⑥	7
Liu [12] 2012	3~11	not mention	42/21	OR 1 μg/kg IV over 10 minutes	saline	④⑤⑥	1
Zhang [13] 2010	2~8	Lower abdominal surgery	40/20	DEX 0.2 μg/kg OR 0.4 μg/kg IV before the end of surgery	saline	⑤	1
Fang [14] 2010	3~10	Oral and ENT surgery	30/30	DEX 0.3 μg/kg OR 0.5 μg/kg IV after the start of surgery	saline	②⑤⑥	1
Wen [15] 2012	3~11	Oral and ENT surgery	30/30	DEX 0.5 μg/kg IV before the surgery	saline	①⑤⑥	1
Cao [16] 2012	3~6	High ligation of the hernia sac and circumcision	40/20	DEX 0.5 μg/kg IV before the surgery	saline	⑤	1
Zhu [17] 2011	3~8	adenoidectomy	40/40	DEX 0.5 μg/kg OR 0.7 μg/kg,iv	saline	①②③④⑤⑥	2
Zhu [18] 2012	3~8	Laryngeal papilloma resection	30/30	DEX 0.5 μg/kg IV before anesthesia induction	saline	①②③④⑤⑥	2
Du [19] 2012	3~9	Inguinal hernia repair and circumcision	28/28	DEX 0.5 μg/kg IV before anesthesia induction	saline	①⑤	1
Gan [20] 2011	4~7	ENT surgery	150/150	DEX 1 μg/kg IV after the start of surgery	saline	②⑤	2
Xue [21] 2011	3~9	Oral, Ophthalmologic, abdominal surgery	40/40	DEX 0.5 μg/kg IV before anesthesia induction	saline	②⑤	1
Jia [22] 2012	2~7	adenoidectomy	30/30	DEX 0.5 μg/kg IV after the start of surgery	saline	①②⑤⑥	6
Jin [23] 2011	3~12	Ophthalmologic operation	40/40	loading dose: DEX 1 μg/kg, 1 μg/kg/h to maintain	saline	①③⑤⑥	1
Zhong [24] 2012	4~10	tonsillectomy	40/40	DEX 1 μg/kg IV after tracheal intubation	saline	①②⑤⑥	2
Chen [25] 2012	2~8	High ligation of the processus vaginalis	15/15	loading dose: DEX 0.1 μg/kg, and 0.3 μg/kg/h to maintain	saline	②③⑤⑥	2
Wei [26] 2012	3~7	Inguinal hernia repair	46/23	DEX 1 μg/kg IV before anesthesia induction	saline	①⑤	1
Huang [27] 2012	1~3	cleft lip and cleft palate repair	15/15	DEX 0.15 μg/kg OR 0.3 μg/kg IV before the surgery	saline	①⑤	1
Huang [28] 2011	5~8	Hypospadias and ENT surgery	30/30	DEX 1 μg/kg IV, 30 min before the end of surgery	saline	①②⑤	1
Zhao [29] 2012	2~8	High ligation of the hernia sac and Orchidopexy	20/20	DEX 0.2 μg/kg IV, 30 min before the end of surgery	saline	①②⑤⑥	1
				DEX 1 μg/kg, iv			

Note: ① recovery time ② extubation time ③ discharge time ④ occurrence of bucking ⑤ emergence agitation or agitation score ⑥ other adverse events

Table 1: Characteristics of included studies and Jadad score.

Collaboration was used for analysis. We computed the Relative Risk (RR) with corresponding 95% confidence intervals (95%CI) for dichotomous outcome data, and Mean Difference (MD) with 95% CI for continuous outcomes data, using a fixed-effect model, if there were no heterogeneity present. Otherwise, a random-effects model was applied. Heterogeneity was judged with the I^2-test, assuming heterogeneity if an I^2 value of more than 25% was observed. If severe heterogeneity was presented ($I^2 \geq 75\%$) and could not be explained by differences across the trials in terms of clinical or methodological features or by subgroup analysis, we did not combine the trials in the meta-analysis, but presented the results in a forest plot. Removal the low-quality literature for sensitivity analysis. If more than 10 trials were included: a funnel plot was used to assess publication bias. A P-value<0.05 was used to determine statistical significance.

Result

The basic characteristics of the included studies

Using electronic databases, we initially identified 216 articles for review after reading title, abstract and full text based on the inclusion and exclusion criteria and ultimately left 27 RCTs with 9 English articles and 18 Chinese articles, a total of 1882 pediatric patients were included. The basic characteristics and quality of the selected trials were summarized in Table 1 [3-29].

Meta-analysis results

Recovery time: Sixteen RCTs (948 children) provided data on recovery time. The heterogeneity test showed a severe heterogeneity among the trials, a random-effects model was applied, the results showed that compared with placebo, dexmedetomidine extended the recovery time [MD=2.39, 95% CI (1.27, 3.51)], [4,5,9-11,15-19,22-28] (Figure1).

Sensitivity analysis: exclude low-quality literature with modified Jadad score less than 3 points to redo a meta-analysis, there were no heterogeneity present among the groups, so we used a fixed-effect model for Meta-analysis, the outcome remained similar [MD=1.39,95% CI (0.65,2.13)].

Extubation time: Sixteen RCTs (1183 children) compared both extubation time. There was no statistically significant heterogeneity present among the groups, so we used a fixed-effect model for statistical analysis, the results showed no statistically significant difference between DEX and placebo group [MD=0.75, 95% CI (0.45, 1.05)] [4-6,9-11,14,17,18,20-22,24,25,28,29] (Figure 2).

Sensitivity analysis: Exclude low-quality literature with modified Jadad score less than 3 points to redo a meta-analysis, there was still no statistically significant difference between the two groups [MD=0.95, 95% CI (0.27,1.63)].

Funnel plot analysis: no obvious asymmetric distribution, suggesting that little possibility of the publication bias (Figure 3).

Recovery room residence time (discharge time): Eight RCTs (447 children) compared both discharge time. There was significant heterogeneity among the 8 studies. Thus, a random-effects model was used for these statistical analyses. The results are shown: Compared with placebo, dexmedetomidine extended the recovery room

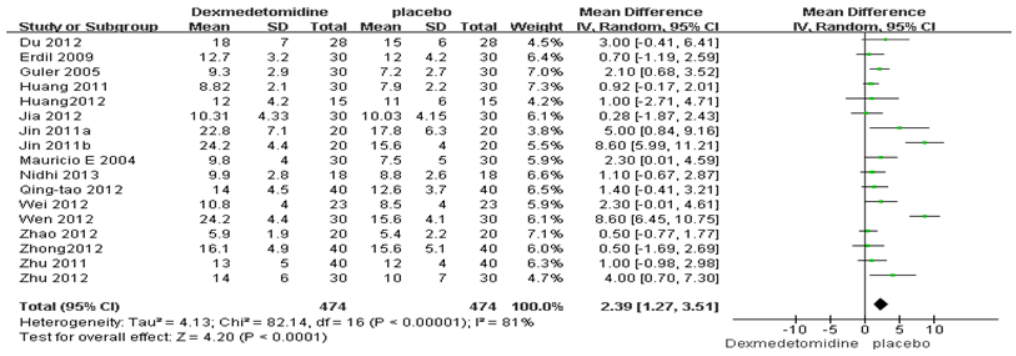

Figure 1: Effect of dexmedetomidine on children's recovery time.

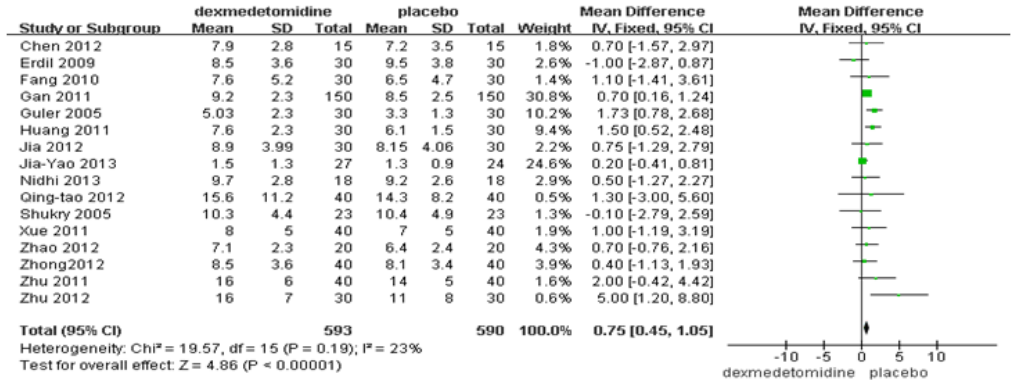

Figure 2: Effect of dexmedetomidine on extubation time.

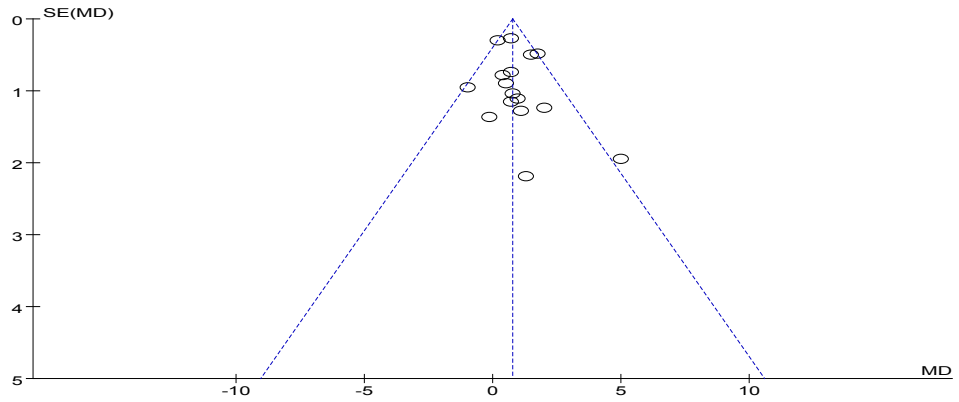

Figure 3: Funnel plot analysis of the 16 studies reporting extubation time.

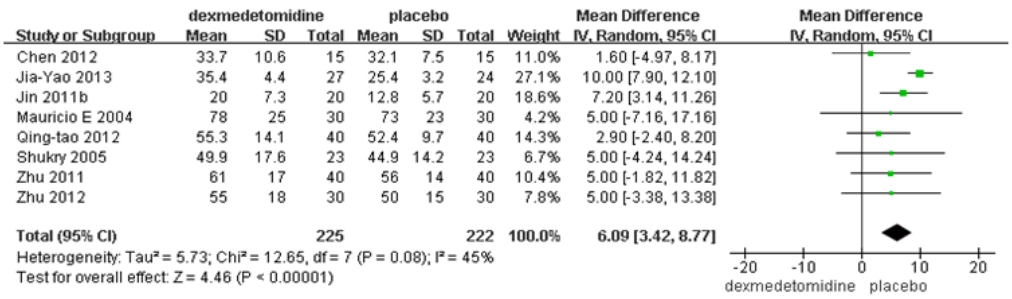

Figure 4: Effect of dexmedetomidine on discharge time.

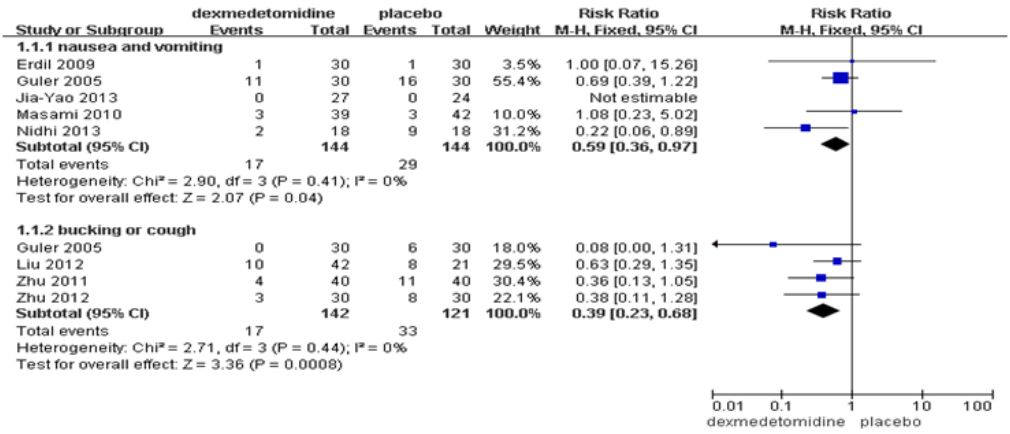

Figure 5: Effects of dexmedetomidine on cough, nausea and vomiting.

residence time [MD=6.09, 95% CI (3.42, 8.77)], as shown in Figure 4 [6,8,9,11,17,18,23,25].

Sensitivity analysis: exclude low-quality literature and redo statistical analysis, the outcomes remained similar [MD=6.57, 95% CI (1.99, 11.15)].

Cough, nausea and vomiting

There are 4 studies and 5 studies which compared DEX with placebo about the incidence of cough or nausea and vomiting. No heterogeneity present in each group, the results showed: dexmedetomidine reduced the occurrence of cough [RR=0.39, 95% CI (0.23, 0.68)] and the occurrence of nausea and vomiting [RR=0.59, 95% CI (0.36, 0.97)] (Figure 5) [4-7,10,12,17,18].

Pain score

Four studies adopt "mean ± SD" pattern to provide data on pain score. A severe heterogeneity among studies, a random-effects model was used for meta-analysis, the results showed that DEX can reduce pain score [MD=-2.66, 95% CI (-3.81, -1.51)], [10,11,17,29] (Figure 6).

The demand of painkillers

Six studies compared DEX with placebo on children' demand

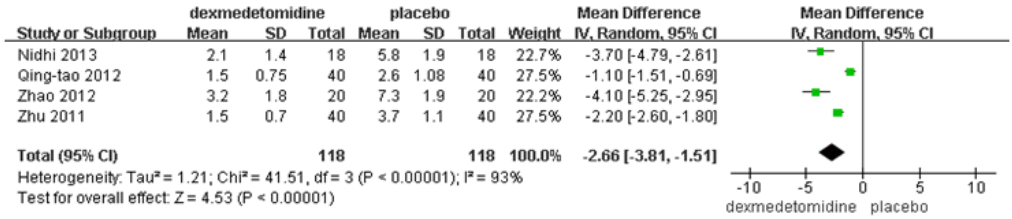

Figure 6: Effect of dexmedetomidine on pain score.

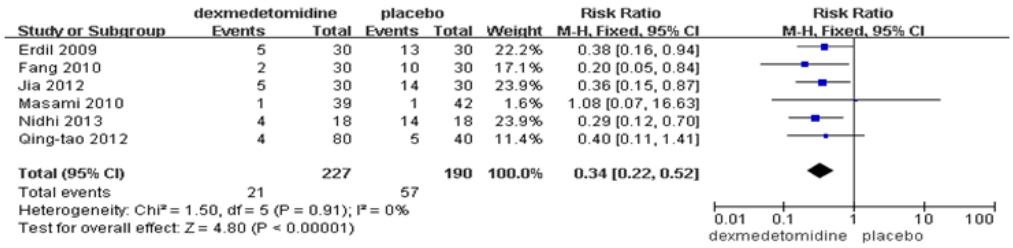

Figure 7: Effect of dexmedetomidine on children's demand of painkillers.

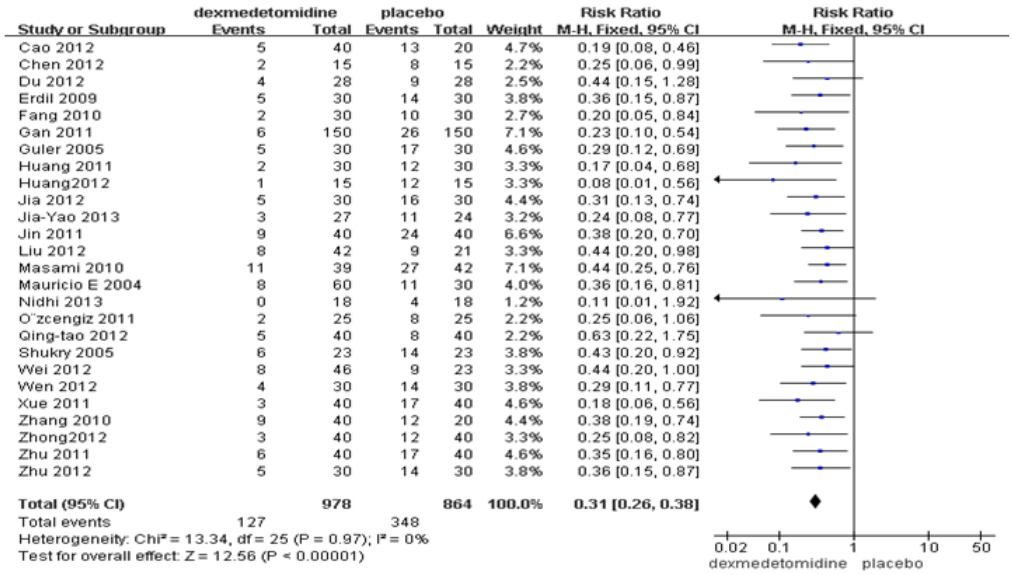

Figure 8: Effect of dexmedetomidine on children's early emergence agitation.

for the painkillers, no statistically significant heterogeneity appeared among the groups, so a fixed-effect model for statistics analysis was used. Results: DEX can reduce children' demand for the painkillers [RR=0.34, 95% CI (0.22, 0.52)] [4,7,10,11,14,22] (Figure 7).

Emergence agitation

Twenty-six studies compared DEX with placebo over the incidence of early emergence agitation in recovery room. No statistically significant heterogeneity appeared among the groups, a fixed-effects model used for statistical analysis. The results showed that dexmedetomidine can significantly reduce the incidence of emergence agitation [RR=0.31, 95% CI (0.26, 0.38)] [3-28] (Figure 8).

Sensitivity analysis: the analysis excluded low-quality literature and redo statistical analysis, the outcomes remained similar [RR=0.36, 95% CI (0.27, 0.48)].

Funnel plot analysis: there were no obvious asymmetric distributions, suggesting that little possibility of the publication bias (Figure 9).

Agitation score

Seven studies adopt "mean ± SD" pattern to provide data on agitation score, statistical analysis shows: DEX can reduce the patients' agitation score [MD=-0.89, 95% CI (-1.04, -0.74)] (Figure 10) [3,10,11,17,18,25,29].

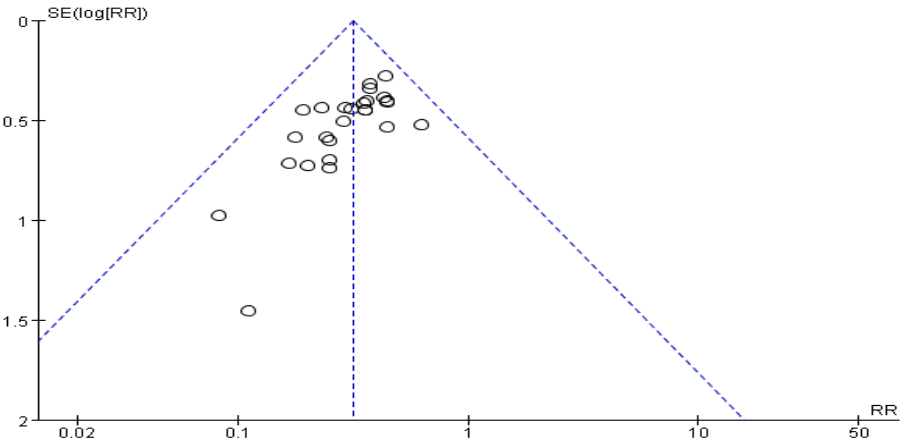

Figure 9: Funnel plot analysis of the 26 studies reporting early emergence agitation.

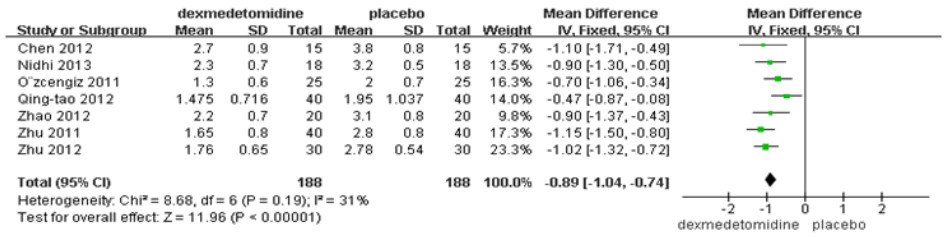

Figure 10: Effect of dexmedetomidine on agitation score.

Discussion

Pediatric surgery is usually featured with small scale, short operational time and length of stay, and fewer complications, etc [30]. Therefore, recovery time and the incidence of postoperative complications are important indicators for the evaluation of pediatric anesthesia. How to improve the recovery quality of anesthesia and reduce the incidence of complications in recovery period, and shorten the residence time in the operating room or PACU, is a focus attention for anesthesiologists in recent years.

This study included 27 RCTs involving 1,882 children. These RCTS are measured by key words such as the recovery time, extubation time, discharge time, the incidence of early emergence agitation, the occurrence of cough, nausea and vomiting, pain score, agitation score and the need for painkillers respectively and then rates one by one for statistical pooled analysis one by one. The results of the meta-analysis showed that compared with placebo saline, dexmedetomidine can extend the recovery time and discharge time, while the time of extubation was no significant difference, dexmedetomidine can significantly reduce the incidence and the severity of the early postanesthetic emergence agitation, children's need for painkillers, and DEX may play a preventive role in decreasing the occurrence of nausea and vomiting, choking cough. What's more, the hemodynamic in Perextubate period was steady in the 27 trials, and without one case of respiratory and circulatory system complications.

As mentioned above, Sevoflurane is widely used in pediatric anesthesia now. However, sevoflurane may be associated with a high incidence of emergence agitation and is observed more frequently in preschool aged children. A study by Sanford et al. reported that the occurrence of emergence agitation in children after sevoflurane anesthesia may be as high as 67%. Another study reported the agitation occurrence rate range from 18% to 80%. In this article, we included 27 trials, which were divided into two groups [31]. In placebo group, 864 children, the number of patients with emergence agitation reached 348, and the incidence is as high as 40.3%. In dexmedetomidine group the incidence is only 13.0%. Though emergence agitation is mostly self-limiting, severe cases can affect surgical outcomes, and cause a great impact on children's physical and psychological health; therefore children's postoperative agitation after sevoflurane anesthesia has become a concern of clinicians focus.

Dexmedetomidine is a novel highly selective α2-adrenergic receptor agonist, the α2:α1 activity ratio of DEX is 1620:1 compared with 220:1 for clonidine, this results in a more specific and selective α2-adrenoceptor agonism. It can affects the brain and spinal cord alpha 2 adrenergic receptor, inhibition of neural discharge to produce sedative, analgesic, anxiolytic effects. The Locus Coeruleus is a verified key part of the brain responsible for the regulation of arousal and sleep. Dex affects the brainstem locus coeruleus alpha 2 adrenergic receptors, produces sedative, hypnotic, and anxiolytic. Compared with the benzodiazepine, DEX also reduces the movement of the stomach and intestines, and inhibits glandular secretion as well as reducing the incidence of postoperative nausea and vomiting. In addition, DEX can inhibit sympathetic activity, reduces plasma epinephrine and norepinephrine levels and maintain hemodynamic stability. DEX sedative effect is unique in many ways, and has a dose-dependent manner [32]. Moreover, DEX has no addiction, and has a very slight respiratory inhibition. Based on all the advantages of the dexmedetomidine and the comprehensive statistical analysis results of this study, we have reason to believe that, the combination of dexmedetomidine and sevoflurane will be more widely used for the future pediatric surgeries.

Although our study does find some significant things, our review also has some limitations. First, among the 27 RCTs, although the 9 English articles can get 6 to 7 score from the modified Jadad scale score, and belong to high-quality literature. While the 18 Chinese articles belong to low-quality literature, the main problem was that these studies have not report the concealment of the allocation scheme and the random method, may exist a selection bias; unused blinded, may result in the presence of observer bias. Second, dexmedetomidine dosage was different from 0.1 to 1 μg/kg, usage ranging from preoperative and intraoperative. Third, in some ill-defined text, each hospital or researcher may not has a same standardization for test or record such as recovery time, the different grasp of the timing of the recovery, extubation and discharge time may have contributed to the heterogeneity between each experiment. In this case, we still should carefully look at the above meta-analysis conclusion.

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